Aplasia of the bone marrow was seen in two-thirds of the patients. It was preceded by a rapidly developing pancytopenia. The bone marrow may show large cells similar to lymphoblasts soon after rubidomycin is given. These cells may persist throughout the aplastic phase. Their presence should not be taken as an indication that more rubidomycin is necessary but rather that the phase of aplasia is imminent or that remission is beginning.

Other toxic effects included alopecia and pruritus. No neurotoxicity or renal or liver damage has been seen.

It is important not to start maintenance therapy too soon after remission has been achieved. One of the patients (Case 9) went through a severe aplastic phase and then entered remission but became aplastic when given mercaptopurine before the peripheral blood count had returned to normal. Maintenance therapy is now begun when the peripheral white cell count is above 2,000/cu. mm.

A summary of the results of treatment is given in Table II.

TABLE II

Type	No.	Remission	Partial Remission	Failure
ALL	3	1	1	1
AM	1	0	0	1
AMM	2	0	1	1
Treated AML	8	2	0	6
Untreated AML ..	8	1	0	7
Total	22	4	2	16

We should like to acknowledge the helpful advice given to us by Professors J. Bernard and G. Mathé during the introduction of this drug for clinical use. We also wish to acknowledge the co-operation of Dr. D. A. Chamberlain and Dr. J. S. Fleming in evaluation of the electrocardiograms. We are grateful to Dr. G. Hamilton Fairley for allowing us to include some of his patients and to Dr. J. Nuttall-Smith, of May & Baker Ltd., for supplies of Cerubidin brand of rubidomycin.

J. S. MALPAS, M.B., B.SC., D.PHIL., M.R.C.P.
Sir RONALD BODLEY SCOTT, K.C.V.O., M.A., D.M., F.R.C.P.
St. Bartholomew's Hospital,
London.

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Medical Memoranda

Collapse after Intravenous Injection of Hashish

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Much interest centres on the increasing and illicit use of hashish. Most devotees smoke and a few ingest the resin. The present report describes the results of experimenting with a less orthodox route.

CASE REPORT

A previously fit 22-year-old man was admitted to the Bristol General Hospital on 18 July 1966, having collapsed the previous day after a self-administered intravenous injection of about 10 to 20 ml. of an opalescent brown liquid which he had prepared by boiling hashish with water in a saucepan. He had taken tranylcypromine for two weeks up to 16 July but no other drugs or injections in recent months.

Half an hour after the injection he became suddenly ill with vomiting and diarrhoea, weakness, giddiness, abdominal cramps, blurred and double vision, generalized muscle aching, and peripheral paraesthesiae. The vomiting and diarrhoea continued for 12 hours. The other symptoms resolved following resuscitation 20 hours after the injection, with the exception of the muscle aching and tenderness, which persisted for a further day.

On admission to hospital he was conscious but in severe oligaemic circulatory failure, with intense peripheral vasoconstriction, marked sweating, sinus tachycardia, unrecordable blood pressure, and haemoconcentration. He was icteric, with hepatic enlargement and tenderness. There were no other abnormal physical findings. At no time was pyrexia recorded. Urine contained albumin and bilirubin but no cells or casts.

He was treated with plasma and saline infusions. Intravenous hydrocortisone followed by diminishing doses of oral prednisone for two weeks, and courses of cloxacillin, ampicillin, and vitamin K were given. In the first 24 hours the mean central venous pressure rose from 0 to 15 cm. of water and the brachial artery systolic pressure to 70 mm. Hg. These pressures reached normal levels the next day.

Bouts of hiccups and scanty haemoptysis occurred on the day after admission, and crepitations were heard at the right lung base. Chest *x*-ray examination showed diminished vascular markings at the left base and cardiac enlargement; two days later the left base was normal but there was an opacity in the right posterior basal segment consistent with a pulmonary infarct. Serial electrocardiograms showed the changes of acute severe right ventricular strain, with extreme right axis deviation and right bundle-branch block, followed by deep S–T segment depression over the lateral chest leads and leads aVF, II, and III; these abnormalities rapidly resolved and in 36 hours the tracing was normal.

Haemoglobin concentration was initially 19.4 g./100 ml., falling to normal after fluid replacement. The white blood cell count was 40,000/cu. mm., with polymorph leucocytosis. Transient thrombocytopenia developed, the platelet count falling to 54,000/cu. mm. Blood urea rose from 74 to 220 mg./100 ml. on the third day, after which a spontaneous diuresis began, blood urea fell to normal, and urine no longer contained albumin. The serum bilirubin rose to 8.2 mg./100 ml. and the aspartate aminotransferase to 225 units/ml. on the third day, these levels falling respectively to normal and 170 units/ml. three weeks later. The serum alkaline phosphatase was 22 K.A. units/ml. and the prothrombin time 58% of normal, both reverting to normal within a few days. Serum protein, blood sugar, and serum calcium levels remained normal. Blood cultures were sterile and cultures of faeces and sputum grew no pathogenic organisms.

Despite the severity of the organic disturbance he felt well after two days in hospital and took his own discharge three weeks later.

On 5 December he was readmitted to hospital with a temporary exacerbation of the hepatocellular disturbance after an alcoholic debauch. Liver biopsy showed an increased number of round cells in the portal tracts but an otherwise normal histological appearance.

Analysis of Hashish Decoction

Samples of the aqueous suspension used and the resin from which this had been prepared were examined microscopically. The solids separated from the suspension, the aqueous phase, and the original resin were each analysed by thin layer and gas chromatographic techniques. Extracts were prepared from the solids by double extraction with a hexane–methanol mixture (1 : 1) and subsequent concentration at room temperature. Gas chromatography was performed with an F. and M. Biomedical 400 Gas Chromatograph, equipped with a 6-ft. (1.8-m.) glass column containing 3.8% W 98 on Diatoport S at 200° C., a flame ionization detector, and nitrogen as the carrier gas. Tetrahydrocannabinol and cannabinol were identified by their retention times relative to cannabidiol and by correlation with their thin layer chromatographic characteristics; the results were quantitated by reference to pure cannabidiol, the responses to tetrahydrocannabinol, cannabinol, and cannabidol being assumed to be equivalent on a molecular basis. Thin layer chromatographic analysis was performed with form-dimethylamide-impregnated silica gel plates and cyclohexane as the developing solvent.

The decoction was found to contain 24.7 mg. of undissolved solids per ml., including plant debris having the microscopical characteristics of cannabis and similar to the plant parts present in the solid resin. The suspended particles contained 8.5% by weight of total cannabinols, whereas the original resin contained 4.5%. Less than 2% of the total cannabinols present in the decoction were in aqueous solution. Cannabidiol, tetrahydrocannabinol, and cannabinol were identified in the aqueous solution, cannabidiol being the most soluble constituent, and in both the solid extracts. In addition the solid extracts contained a number of unidentified phenolic substances (Korte and Sieper, 1965). The total cannabinol content of the decoction was similar to, but the tetrahydrocannabinol content about half that of, tincture of cannabis (*B.P.C.*, 1949).

Discussion

Extracts of *Cannabis sativa* are probably more widely available in Britain today than at any time since its properties were first appreciated some 3,000 years ago (Bewley, 1966). The drug is relatively non-toxic (Goodman and Gilman, 1965). The lethal dose is more than 100 times the pharmacologically effective dose, and ranges from 100 to 5,000 mg./kg. body weight (Walton, 1938). Reference to only two human fatalities could be found (G. F. W. Ewens, cited by Walton, 1938, p. 126).

The symptoms of cannabis intoxication are typically abrupt in onset, appearing 20 to 100 minutes after intravenous administration (Loewe, 1944). Somatic manifestations include thirst, nausea, frequency of micturition, sinus tachycardia, peripheral vasoconstriction, faintness, ataxia, peripheral paraesthesiae, difficulty in focusing, and conjunctival congestion. Toxic doses may cause vomiting, diarrhoea, abdominal cramps, vertigo, conjugate deviation of the eyes, hypotension, haemoconcentration, respiratory depression, hypothermia, and collapse (Allentuck, 1944; Sollman, 1957; Ames, 1958; Dagirmanjian and Boyd, 1962; Mohan and Sood, 1964; Miras, 1965; Goodman and Gilman, 1965).

The symptoms and mode of onset in the present case were consistent with cannabis intoxication. However, the estimated intravenous dose of total cannabinols was only 40 mg., of which less than 0.8 mg. was in solution and only a small fraction of this the relatively insoluble active constituent tetrahydrocannabinol. It is likely that the injected particles acted in addition as microemboli, inducing subsequent thromboses. This interpretation is suggested by the delayed onset of symptoms, the evidence of acute pulmonary hypertension and infarction without peripheral venous thrombosis, and the transient thrombocytopenia. The severe circulatory failure produced by a combination of acutely increased pulmonary vascular resistance and fluid loss might then account for many of the clinical features, though the contributory effect of similar vessel occlusion in other organs cannot be excluded.

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A. H. Henderson,* M.B., M.R.C.P.,
David J. Pugsley,† M.B., Ch.B.,
United Bristol Hospitals.

Report on analysis of injected material by

Ann E. Robinson, B.Pharm., Ph.D., F.R.I.C.,
M. R. Page, B.A.,
F. E. Camps, M.D., F.R.C.P.,
‡ Department of Forensic Medicine, the London Hospital Medical College, London E.1.

* Present address: Peter Bent Brigham Hospital, Boston, Massachusetts, U.S.A.
† Present address: Department of Medicine, Mulago Hospital, Kampala, Uganda.
‡ Reprint requests to this address.

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